REMARKS

A. Status of the claims:

Claims 1-19 and 24-27 were previously canceled in the case. Claims 20-23 and 28-30 are currently pending.

B. Rejection of Claims 20-23 as Anticipated by Villalona-Calero *et al.*

The Action rejects claims 20-23 as anticipated by Villalona-Calero. In response, Applicants traverse.

As with the further rejections discussed below, this rejection is necessarily based on a theory of inherency. However, the Examiner is reminded of the current PTO position on inherency, as set forth in the MPEP:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.). >Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the

> claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.<
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> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." *Id.* at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

MPEP, section 2112.

Here, the Examiner has failed to provide a technical reasoning to support a conclusion that the methods for cancer treatment used by Villalona-Claero ***necessarily*** involve "determining whether angiogenesis has been inhibited in said individual" as specified by the claims. This is a basic aspect of the present invention as reflected by all of the claims. Based on this discovery by the present inventors, we now know that CRFR2 agonists can inhibit angiogenesis and, hence, we can now seek to target the ***specific*** tumors that may respond to an inhibition of angiogenesis, through the administration of a CRFR2 agonist.

In fact, Villalona-Calero **does not even suggest the possibility** of the inhibition of **angiogenesis** by a CRFR2 agonist, but rather teaches the unrelated idea that **hCRF inhibits vascular leakage of plasma in patients with peritumoral brain edema**. See, *e.g.*, the first paragraph of the introduction of Villalona-Calero and/or page 2 of the March 31, 2006 BPAI Decision. Further, and as stated above, "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of

circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (MPEP§2112).

Applicants have been unable to identify any explicit or implicit teaching in Villalona-Calero to support the idea that angiogenesis is altered by hCRF. Further, the teaching by Villalona-Calero that hCRF inhibits vascular leakage and the relatively short duration (24 hr or 72 hr) of administration would be recognized by one of skill to indicate acute or immediate effects of hCRF. In particular Applicants note that, as stated on p. 72 of Villalona-Calero, MRI scans were "obtained immediately before starting and repeated at the conclusion of the infusion." As would be appreciated by one of skill, there exists a myriad of possible reasons that an acute effect might be observed on the microvasculature (*e.g.*, changes in ion pumping, membrane function or permeability, homeostasis, hydrostatic pressure, oncotic pressure, sodium retention, *etc.*); however, as would immediately be appreciated by one of skill, a reduction brain edema after administration of a compound for only 24 hours would **not** be assumed by one of skill in the art to imply an alteration in angiogenesis. If anything, Applicants submit that these results would suggest to one of skill that some acute anti-edematous effect (not an alteration in the growth of cells) would be the pharmacological function. Villalona-Calero is specifically silent on the possibility of alterations in angiogenesis.

Applicants agree with the Examiner, as stated on p. 4 of the Action, that Villalona-Calero do not monitor angiogenesis with the MRI scans. Applicants submit that the Actions assertion that an MRI scan could have separately have been used to try to evaluate angiogenesis is irrelevant to the question of whether the MRI scans were used to evaluate angiogenesis. As would be appreciated by one of skill, many if not all medical and laboratory tools may be used in a wide variety of ways. Applicants submit that this argument presented by the Action is

improperly based on hindsight reconstruction and/or possibility that the a tool used in Villalona-Calero (*i.e.*, MRI) could have been separately used for a different purpose or in a different way.

Applicants again submit that the Examiner's inherency argument is misplaced. The Examiner appears to assert that "determining whether angiogenesis has been inhibited" of the claims and Villalona-Calero are the same. This is not true. The claims require "determining whether angiogenesis has been inhibited", yet nowhere that we can find does Villalona-Calero teach such an invention, either expressly or inherently. The fact is, the Examiner has failed to identify where in the Villalona-Calero publication does it teach or suggest to "determine whether angiogenesis has been inhibited."

As stated above, regarding the cited phrase on p. 29 of Villalona-Calero, "hCRF reduces water content in... brain tumor models... This effect appears [to be] a direct effect action the tumor microvasculature." (emphasis added), Applicants note that this phrase merely indicates that some acute action on the microvasculature may be affecting water content; however, this phrase does not give any indication as to what action hCRF may have on the microvasculature. For example, and as stated above, any variety of possible actions on the microvasculature could possibly be affecting the water content of a tissue without affecting vasculature growth or angiogenesis, and, if anything, Applicants submit that the acute effects observed in Villalona-Calero would suggest to one of skill that angiogenesis is not likely involved. Applicants note that this the above cited phrase does not provide any indication that hCRF might affect vasculature growth.

Evaluating changes in the water content of a tumor as performed in Villalona-Calero is distinct from "determining whether angiogenesis has been inhibited" according to the instant

claims. Further, as would be recognized by one of skill, cancers may vary greatly in their responses to therapeutic agents. Thus, it is feasible that the specific cancer tested in Villalona-Calero may not have exhibited significant changes in angiogenesis during the acute timeframe of administration, but rather that changes in the water content of the tumors are due to some other effect of hCRF administration. While, in view of the present invention and using hindsight reconstruction, one might hypothesize that angiogenesis has been inhibited in the tumors treated in Villalona-Calero, Villalona-Calero provides no such specific data to support such an assertion of an effect on angiogenesis. As stated above, Villalona-Calero does not provide the element of "determining if angiogenesis is affected" as required by the instant claims.

Applicants note that Villalona-Calero does not provide any teaching to determine whether or not angiogenesis has been affected by the administration of hCRF. As the instant claims require the determination of whether angiogenesis has been inhibited, Applicants submit that Villalona-Calero does not teach all of the instant claim limitations and thus does not anticipate the instant claims under §102. "A claim is anticipated only if **each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (emphasis added) *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP §2131.

As stated on page 2 of the March 31, 2006 BPAI Decision, "**Villalona-Calero teaches administering a CRFR2 agonist**, specifically human corticotropin releasing factor (hCRF), **to 'inhibit vascular leakage of plasma.'** Page 71, column 2, last paragraph" (emphasis added). Applicants note that the inhibition of the vascular **leakage** of plasma **is distinct from** the inhibition of **angiogenesis**. Withdrawal of the rejection is respectfully requested.

C. Rejection of Claims 20 and 28-30 as Not Enabled

Applicants agree with the Examiner that the present application is enabling for the inhibition of inhibiting angiogenesis in a human individual with cancer. Regarding the rejection of claims 20 and 28-30, Applicants traverse.

In contrast to the Action's assertion that the present application merely provides a *hypothesis* that CRFR2 agonists may inhibit angiogenesis, the present specification provides **direct biological evidence** that CRFR2 is critically involved in angiogenesis in all tissues tested (see, *e.g.*, Abstract, Example 16). The evidence presented in the instant application would be appreciated by one of skill, and Applicants note that *in vitro* evidence is routinely used to support methods for *in vivo* therapies.

Applicants note that the specification clearly states that CRFR2 agonists may be used to inhibit angiogenesis in other diseases such as diabetic retinopathy (*e.g.*, see published paragraph [0025], [0101], *etc.*). Applicants note that §112 is satisfied by a constructive reduction to practice, and §112 does not require an actual reduction to practice. The Action appears to speculate that CRFR2 agonists may not be used to inhibit angiogenesis in other diseases or imply that working example(s) are ***required*** to support additional methods for the administration of a CRFR2 agonist.

To support this assertion, the Action provides the quote that "**Possibly, *mechanisms driving*** the angiogenic cascade are differentially regulated depending on the disease pathology" (emphasis added, Griffioen *et al.*). Applicants submit that this argument is irrelevant to the claimed invention because it appears to assume that an **equivalent mechanism of arriving at a disease state** must be exhibited by a disease state in order to achieve some benefit from a therapeutic. For example, as would be appreciated by one of skill, the reason(s) or mechanism

for the emergence of some aspect of a disease state (*e.g.*, a headache) do not need to be identical for the alleviation of some aspect of the disease state by a therapeutic (*e.g.*, an asprin). As would be appreciated by one of skill, a myriad of different underlying biological phenomena or causes may contribute to the emergence of a disease state (*e.g.*, unwanted angiogenesis) which can be treated by a therapeutic which may function via a pathway **unrelated to the emergence** of the disease state; indeed, many if not most chemotherapeutics function via mechanisms which are unrelated to the emergence of the cancer itself. As would further be appreciated by one of skill, the inhibition of angiogenesis (*e.g.*, by a CRFR2 agonist) may be therapeutically utilized to treat a variety of disease states which would benefit from an inhibition of angiogenesis.

Applicants note that the cited quotation regarding thrombospondin-1 presented in Griffioen *et al.* (on p. 262, left column) describes the effects of this compound on the disease parameters in tumor growth-induced angiogenesis as compared the chronic inflammatory disease arthritis. Applicants submit that the implication of this passage relates to the question of whether it is prudent for a clinician to administer an angiogenesis inhibitor to ameliorate the symptoms of a given disease, not whether or not angiogenesis inhibitors can inhibit angiogenesis in a variety of disease states. Indeed, Applicants note that the first sentence of this paragraph states, "Many of the above considerations on tumor-directed antiangiogenic therapies seem to be applicable to chronic inflammatory disease." (Emphasis added, Griffioen *et al.* p. 262, left column.) Applicants thus submit that the quoted passage is irrelevant to the question as to whether the present invention provides a sufficient written description and enablement of inhibition of angiogenesis via a CRFR2 agonist in a disease other than cancer.

The Action has not provided any substantial reason to question the enablement of the present disclosure as it related to the inhibition of angiogenesis in disease states other than cancer.

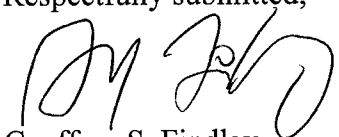
Applicants note the burden on the Examiner regarding the Enablement requirement under MPEP§2164.01. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." (emphasis added) 439 F.2d at 224, 169 USPQ at 370. In the current case, the element asserted to be lacking is both disclosed in the specification and known in the art.

Applicants further note the test for enablement, as explained in MPEP§2164.01. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). As stated in Griffioen et al. on p. 238, "With increasing insight into the role of angiogenesis in other [non-cancerous] diseases as well, modulation of vascular outgrowth is now regarded as a therapeutic target in these diseases." (Emphasis added.) Clearly, the inhibition of angiogenesis via a CRFR2 agonist in a disease other than cancer could be performed without undue experimentation by one of skill in the art in possession of the specification.

Conclusion

It is submitted that in light of the foregoing, it can be seen that the claims are in a condition for allowance. The Examiner should feel free to contact the undersigned should any questions arise.

Respectfully submitted,



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